LETTERS

Development of new-onset psoriasis while on anti-TNFα treatment

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Treatments directed against the proinflammatory cytokine tumour necrosis factor α (TNFα) are effective in rheumatoid arthritis and spondyloarthropathies. In patients with inflammatory arthritis secondary to psoriasis, chronic skin plaques also resolve with this treatment. We report on a series of clinical cases in which, conversely, there was a first presentation of psoriasis while on anti-TNF treatment.

The first case is that of a 49-year-old man with established ankylosing spondylitis, who was started on infliximab and showed an excellent response. After 8 months of treatment, he developed an erythematous, pustular rash over his back (fig 1). No clinical or serological evidence of infection was found and his medication, including methotrexate, was stable.

Although antinuclear antibodies were positive, the rash was not suggestive of photosensitivity. Histological examination of the lesion showed that it was consistent with acute pustular psoriasis (fig 2), which resolved by increasing the methotrexate dose.

The second case was that of a 68-year-old woman with psoriatic arthritis (PsA), who was started on infliximab, with initial resolution of her plaque psoriasis and inflammatory arthritis. She subsequently developed a new variant of psoriasis that was flexural, affecting her axillae and groin. This resolved with topical treatments.

The final case is that of a 54-year-old woman with seropositive rheumatoid arthritis, who was started on adalimumab. After 10 months of treatment, she developed hyperkeratotic skin lesions consistent with guttate psoriasis.

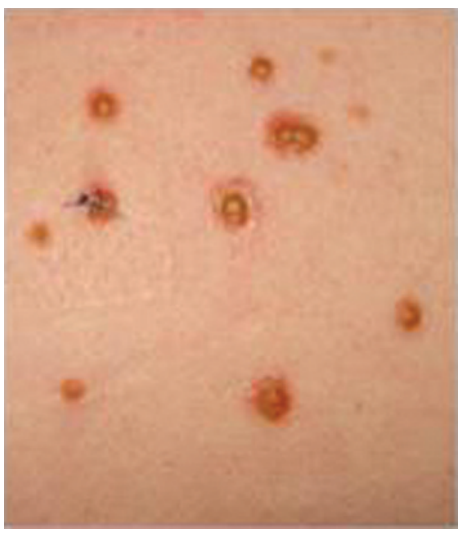

Figure 1 Vesicular rash on the patient's back. The lesions formed small pustules on a red base with areas of encrustation. The eruption suggested pustular psoriasis.

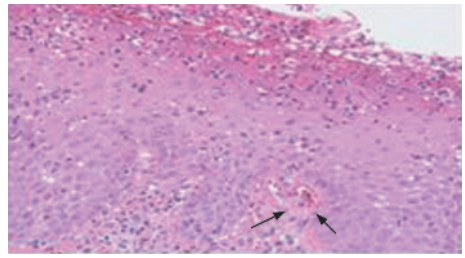

Figure 2 Haematoxylin and eosin stain of skin lesion showing orthokeratosis of the epidermis, with perivascular lymphocytic infiltrate in the superficial papillary dermis. Neutrophils in the superficial stratum spinosum are consistent with acute psoriasis.

There was a positive family history of plaque psoriasis. Her rash completely resolved with conservative management.

Blockade of TNFα is an effective treatment for recalcitrant plaque psoriasis.[1–3] In contrast, we report three cases in which anti-TNF treatment is associated with new-onset psoriasis. The psoriasis phenotype varied between pustular, flexural or guttate, respectively. The exact aetiology of this is unclear. It may represent asymptomatic infection. Guttate psoriasis may be precipitated by Group A β-haemolytic streptococcal infection, where superantigens are hypothesised to play a part in disease pathogenesis.[4] Triggering by varicella zoster has been reported.[5] Colonisation of skin by microbes, including yeasts and gut flora, may have a role in the pathogenesis of psoriasis.[6] Therefore, anti-TNF treatment may predispose a susceptible person to the development of psoriasis triggered by common, commensal organisms.

The development of psoriasis is probably multifactorial. The association of ankylosing spondylitis with psoriasis is recognised. In the patient with a diagnosis of rheumatoid arthritis, there was a family history of psoriasis, suggesting that there was an additional genetic risk.[7]

The development of new-onset psoriasis in patients on anti-TNF treatment is not common.[8] We describe three cases out of approximately 400 patients who have been treated since 1999. The effect of TNF blockade, combined with other precipitating factors, seems to occasionally result in dysregulation of T cells in the epidermis and increased keratinocyte proliferation, with the subsequent development of psoriasis.

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Informed consent was obtained for publication of the patients' details in this report.

Abbreviation: TNF, tumour necrosis factor

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REFERENCES

1 **O'Quinn RP**, Miller JL. The effectiveness of tumor necrosis factor alpha antibody (infliximab) in treating recalcitrant psoriasis: a report of 2 cases. *Arch Dermatol* 2002;**138**:644–8.
2 **Nikas SN**, Voulgari PV, Takalou IP, Katsimbri P, Drosos AA. Healing of psoriatic skin lesions, and improvement of psoriatic arthritis resistant to immunosuppressive drugs, after infliximab treatment. *Ann Rheum Dis* 2005;**64**:1665–7.
3 **Leonardi CL**, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, *et al*. Etanercept monotherapy in patients with psoriasis. *N Eng J Med* 2003;**345**:248.
4 **Valdimarsson H**, Baker BS, Jonsdottir I, Powles A, Fry L. Psoriasis: a T cell mediated autoimmune disease induced by streptococcal superantigens? *Immunol Today* 1995;**16**:145–9.
5 **Ito T**, Furukawa F. Psoriasis guttate acuta triggered by varicella zoster virus infection. *Eur J Dermatol* 2000;**10**:226–7.
6 **Skinner RB**, Rosenburgh EW, Noah PW. Antimicrobial treatment of psoriasis. *Dermatol Clin* 1995;**13**:909–13.
7 **Naldi L**, Peli L, Parazzini F, Carrel CF. Family history of psoriasis, stressful life events and recent infectious disease are risk factors for a first episode of acute guttate psoriasis: results of a case- control study. *J Am Acad Dermatol* 2001;**44**:433–8.
8 **Sfikakis PP**, Iliopoulos A, Elezoglou A, Kittas C, Stratigos A. Psoriasis induced by anti-TNF therapy: a paradoxical adverse reaction. *Arthritis Rheum* 2005;**52**:2513–8.

Refractory auto-inflammatory syndrome associated with digenic transmission of low-penetrance tumour necrosis factor receptor-associated periodic syndrome and cryopyrin-associated periodic syndrome mutations

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Two dominant periodic fevers, tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) and cryopyrin-associated periodic syndrome (CAPS), are prominent auto-inflammatory disorders. Mutations in the 55 kDa TNF receptor superfamily 1A gene (*TNFRSF1A*) and in the cold-induced auto-inflammatory syndrome 1 gene (*CIAS1*) were recently associated with TRAPS[1] and CAPS,[2] respectively. Following publications describing the efficacy of etanercept (enbrel), a recombinant human TNF receptor 1B fusion protein in patients with TRAPS[3] and anakinra (kineret), a recombinant human interleukin-1 (IL1)-receptor antagonist, in patients with CAPS,[4] targeted biotherapies have been repeatedly and successfully given for these two conditions.

Our proband (fig 1) is a 36-year-old French woman who presented with rashes of urticaria and oedema precipitated by exposure to heat and water. These rashes, lasting a few hours and recurring twice a month since the patient was 6 years old, were associated with moderate fever, symmetric arthralgia of the wrists, ankles and hip, myalgia, painful cutaneous contact, bipolar aphthosis, intense fatigue and conjunctivitis. She had no uveitis, no folliculitis and no pathergy, ruling out Behçet's disease. Levels of C reactive protein were repeatedly found to be normal. Her mother, now aged 60 years, exhibited the same symptomatology, except that she had no genital aphthosis and no urticaria and her oedemas were triggered by both cold and heat. She also showed severe bilateral deformation of the distal interphalangeal joints. The proband's daughter, aged 8 years, had fever, urticaria and oral aphthosis. Because these phenotypes overlapped with symptoms reported for TRAPS and CAPS, we first sequenced *TNFRSF1A* exons 2–4 and *CIAS1* exon 3, thereby covering 98% of the known mutations in both genes. We discovered double heterozygosity for R92Q and V198M in both the proband and her mother. No mutation was found in the two other periodic fever genes: *MEFV* responsible for familial Mediterranean fever and *MVK* responsible for the hyper immunoglobulin D syndrome (not shown). Although the IL1-receptor antagonist has been consistently shown to dramatically improve CAPS, and sometimes TRAPS, in patients within hours of the first injection, the proband's symptoms did not decrease even after 1 month of daily subcutaneous injections of 100 mg anakinra. Instead, she needed to be hospitalised for severe side effects, including fatigue, erythema and anaemia. Four weeks later, she was given etanercept 25 mg subcutaneous

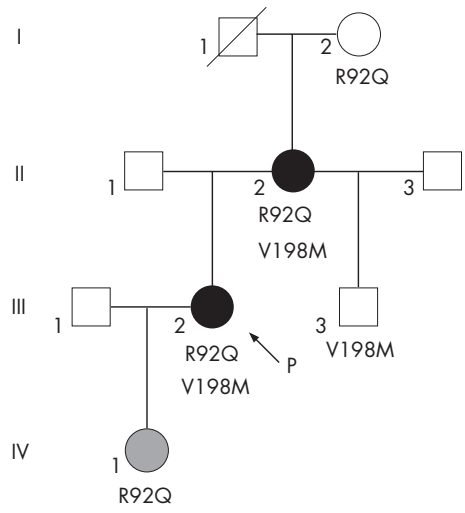

Figure 1 Digenic expression of tumour necrosis factor receptor-associated periodic syndrome and cryopyrin-associated periodic syndrome mutations. The two patients with the most severe phenotypes (black circles), including the proband (P, arrowed), who is refractory to anakinra, inherited both tumour necrosis factor receptor superfamily 1A gene (R92Q) and cold-induced auto-inflammatory syndrome 1 (V198M) mutations. By contrast, two of the three people with only one variant, the grandmother (R92Q) and the step-brother (V198M), were completely asymptomatic. The daughter (grey circle, R92Q) had a milder symptomatology.